Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	6	roller adj peter	US-PGPUB; USPAT; DERWENT	OR	ON	2005/01/20 16:55
L2	7	yang adj dajun	US-PGPUB; USPAT; DERWENT	OR	ON	2005/01/20 16:55
L3	69	lung near Feng	US-PGPUB; USPAT; DERWENT	OR	ON	2005/01/20 16:55
L4	1	l3 and feng near di	US-PGPUB; USPAT; DERWENT	OR	ON	2005/01/20 16:56
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(FILE 'HOME' ENTERED AT 16:58:08 ON 20 JAN 2005)

FILE 'CAPLUS, MEDLINE, USPATFULL, BIOSIS' ENTERED AT 16:58:44 ON 20 JAN 2005

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		E	ROLLER /AU
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L3	0	S	ROLLER /AU
L4	0	S	ROLLER /IN
L5	435061	S	ROLLER
L6	593	S	L5 AND YANG
L7	11	S	L6 AND KING
L8	0	S	ROLLER AND YANG AND KING /AU
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L10	9	S	L9 AND LONG
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		E	L3 /AU
		E	ROLLER /AU
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		E	ROLLER PETER /AU
L13	0	S	E4 AND YANG
L14	274	S	E4
		E	YANG DAJUN /AU
L15	1	S	E4 AND E4
L16	0	S	E4 (L) E3
L17	149	S	E3
L18	37	S	L17 (L) L14
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		E	KING C /AU
L19	388	S	E3
L20	0	S	L19 (L) L18
L21	20	DUP REM	L18 (17 DUPLICATES REMOVED)

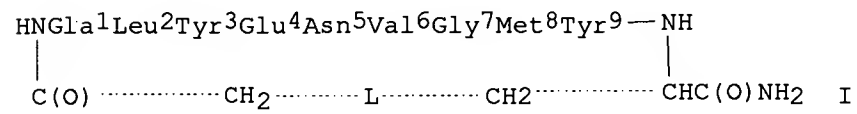
DN 140:399524
TI Discovery of Embelin as a Cell-Permeable, Small-Molecular Weight Inhibitor of XIAP through Structure-Based Computational Screening of a Traditional Herbal Medicine Three-Dimensional Structure Database
AU Nikolovska-Coleska, Zaneta; Xu, Liang; Hu, Zengjian; Tomita, York; Li, Peng; **Roller, Peter P.**; Wang, Renxiao; Fang, Xueliang; Guo, Ribo; Zhang, Manchao; Lippman, Marc E.; **Yang, Dajun**; Wang, Shaomeng
CS Departments of Internal Medicine and Medicinal Chemistry, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, 48109-0934, USA
SO Journal of Medicinal Chemistry (2004), 47(10), 2430-2440
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> dup rem l18
PROCESSING COMPLETED FOR L18
L21 20 DUP REM L18 (17 DUPLICATES REMOVED)

=> d l21 1-10 ti py au so abs

L21 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
TI Discovery of Embelin as a Cell-Permeable, Small-Molecular Weight Inhibitor of XIAP through Structure-Based Computational Screening of a Traditional Herbal Medicine Three-Dimensional Structure Database
PY 2004
AU Nikolovska-Coleska, Zaneta; Xu, Liang; Hu, Zengjian; Tomita, York; Li, Peng; **Roller, Peter P.**; Wang, Renxiao; Fang, Xueliang; Guo, Ribo; Zhang, Manchao; Lippman, Marc E.; **Yang, Dajun**; Wang, Shaomeng
SO Journal of Medicinal Chemistry (2004), 47(10), 2430-2440
CODEN: JMCMAR; ISSN: 0022-2623
AB The X-linked inhibitor of apoptosis (XIAP) is a promising new mol. target for the design of novel anticancer drugs aiming at overcoming apoptosis-resistance of cancer cells to chemotherapeutic agents and radiation therapy. Recent studies demonstrated that the BIR3 domain of XIAP where caspase-9 and Smac proteins bind is an attractive site for designing small-mol. inhibitors of XIAP. Through computational structure-based screening of an in house traditional herbal medicine three-dimensional structure database of 8221 individual natural products, followed by biochem. testing of selected candidate compds., the authors discovered embelin from the Japanese Ardisia herb as a small-mol. weight inhibitor that binds to the XIAP BIR3 domain. The authors showed that embelin binds to the XIAP BIR3 protein with an affinity similar to that of the natural Smac peptide using a fluorescence polarization-based binding assay. The authors NMR anal. further conclusively confirmed that embelin interacts with several crucial residues in the XIAP BIR3 domain with which Smac and caspase-9 bind. Embelin inhibits cell growth, induces apoptosis, and activates caspase-9 in prostate cancer cells with high levels of XIAP, but has a minimal effect on normal prostate epithelial and fibroblast cells with low levels of XIAP. In stably XIAP-transfected Jurkat cells, embelin effectively overcomes the protective effect of XIAP to apoptosis and enhances the etoposide-induced apoptosis and has a minimal effect in Jurkat cells transfected with vector control. Taken together, the results showed that embelin is a fairly potent, nonpeptidic, cell-permeable, small-mol. inhibitor of XIAP and represents a promising lead compound for designing an entirely new class of anticancer agents that target the BIR3 domain of XIAP.

L21 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
TI Redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein, conjugates thereof, compositions, methods of synthesis, and use
PY 2003
2000
2001
IN **Roller, Peter P.**; Long, Ya-Qiu; Lung, Feng-Di T.; King, C. Richter; **Yang, Dajun**
SO U.S. Pat. Appl. Publ., 10 pp., Cont.-in-part of Appl. No. PCT/US00/15201.
CODEN: USXXCO
GI



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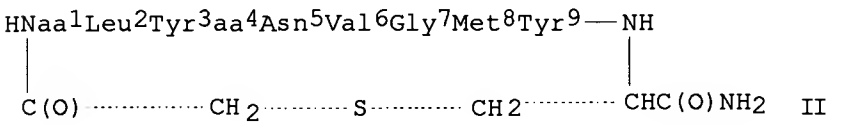


II

AB The invention provides I (L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Glu4, Val6, Met8 and Tyr9 is modified). Also provided are compds. II [aa1 = Adi and aa4 = Glu, or each of aa1 and aa4 = Adi; L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Val6, Met8 and Tyr9 is modified]. Compds. I and II (and their conjugates) bind to an SH2 domain in a protein comprising an SH2 domain, are non-phosphorylated, are redox-stable in vivo, and are characterized by an IC50 in vivo of less than about 4.0 < mM with respect to the SH2 domain in Grb2. Upon binding to the SH2 domain of Grb2, a compound as described above has a turn conformation. Also provided are a conjugate comprising a compound as described above and a carrier agent, a composition comprising (i) a compound or a conjugate as described above and (ii) a carrier, a method of inhibiting binding of an SH2 domain in a protein comprising an SH2 domain to a target protein in an animal, where the SH2 domain is contacted with a target protein-binding inhibiting effective amount of a compound or a conjugate as described above, and a method of synthesizing such conjugates. Thus, cyclo(CH2CO-Adi1-Leu2-Tyr3-Glu4-Asn5-Val6-Gly7-Met8-Tyr9-Cys)-amide was synthesized by the solid-phase method and showed IC50 = 3.45 ± 0.15 for binding affinity to the SH2 domain of Grb2.

L21 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
TI Concise and Enantioselective Synthesis of Fmoc-Pmp(But)2-OH and Design of Potent Pmp-Containing Grb2-SH2 Domain Antagonists
PY 2003
AU Li, Peng; Zhang, Manchao; Peach, Megan L.; Liu, Hongpeng; **Yang, Dajun; Roller, Peter P.**
SO Organic Letters (2003), 5(17), 3095-3098
CODEN: ORLEF7; ISSN: 1523-7060
AB L-Phosphonomethylphenylalanine (L-Pmp) is an important phosphatase-resistant pTyr analog. A most concise and stereoselective approach to the synthesis of the suitably protected Fmoc-Pmp(But)2-OH was developed in order to incorporate the functionally significant L-Pmp residue into peptides and peptidomimetics efficiently using standard Fmoc

protocol. With this key building block, we are able to efficiently synthesize a series of potent Pmp-containing Grb2-SH2 domain antagonists, which can be used as chemotherapeutic leads for the treatment of erbB2-overexpressed breast cancer.

L21 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 4
TI Potent Grb2-SH2 domain antagonists not relying on phosphotyrosine mimics
PY 2003
AU Li, Peng; Zhang, Manchao; Long, Ya-Qiu; Peach, Megan L.; Liu, Hongpeng; **Yang, Dajun**; Nicklaus, Marc; **Roller, Peter P.**
SO Bioorganic & Medicinal Chemistry Letters (2003), 13(13), 2173-2177
CODEN: BMCLE8; ISSN: 0960-894X
AB Development of Grb2-SH2 domain antagonists is an effective approach to inhibit the growth of malignant cells by modulating Grb2-related Ras signaling. We report here potent Grb2-SH2 domain antagonists that do not rely on phosphotyrosine or its mimics. These non-phosphorylated antagonists were developed and further modified by constraining the backbone conformation and optimizing amino acid side chains of a phage library-derived peptide, G1TE. After extensive SAR studies and structural optimization, a non-phosphorylated peptide was discovered with an IC50 of 75 nM. This potent peptidomimetic provides a novel template for the development of non-pTyr containing Grb2-SH2 domain antagonists and acts as a chemotherapeutic lead for the treatment of erbB2-related cancer.

L21 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5
TI Structural basis for a non-phosphorus-containing cyclic peptide binding to Grb2-SH2 domain with high affinity
PY 2003
AU Li, Peng; Zhang, Manchao; Peach, Megan L.; Zhang, Xiaodong; Liu, Hongpeng; Nicklaus, Marc; **Yang, Dajun**; **Roller, Peter P.**
SO Biochemical and Biophysical Research Communications (2003), 307(4), 1038-1044
CODEN: BBRCA9; ISSN: 0006-291X
AB Blocking the interaction between phosphotyrosine (pTyr)-containing activated receptors and the Src homol. 2 (SH2) domain of the growth factor receptor bound protein 2 (Grb2) is considered to be an effective and non-cytotoxic strategy to develop new anti-proliferative agents due to its potential to shut down the Ras activation pathway. Generally, the pTyr-X-Asn minimal binding motif is required for a high-affinity ligand binding to the Grb2-SH2 domain. Using phage-display techniques, we discovered a non-pTyr-containing cyclic peptide G1 with moderate binding affinity from 107 different sequences. To understand the structural basis for the high-affinity binding of these novel non-phosphorus-containing inhibitors to the Grb2-SH2 domain, we extensively studied herein the unique functional requirements of the acidic side chain in Tyr-2 position due to the absence of the phosphate group in these non-phosphorylated peptides. A comprehensive SAR study was also carried out to develop potent Grb2-SH2 domain antagonists based upon this novel template. With both the peptidomimetic optimization of the amino acid side-chains and the constraint of the backbone conformation guided by mol. modeling, we developed several potent antagonists with low nanomolar range binding affinity, such as cyclic peptide 20 with an IC50=0.026 μM, which is one of the most potent non-phosphorus-containing Grb2-SH2 antagonists reported to date. Whole cell assays indicate that peptide 20 can penetrate the cell membranes and inhibit the association of Grb2 with p185erbB2 in erbB2-overexpressing MDA-MA-453 cancer cells at low micromolar concns.

L21 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6
TI Structure-based design of thioether-bridged cyclic phosphopeptides binding to Grb2-SH2 domain
PY 2003
AU Li, Peng; Peach, Megan L.; Zhang, Manchao; Liu, Hongpeng; **Yang,**

Dajun; Nicklaus, Marc; **Roller, Peter P.**
SO Bioorganic & Medicinal Chemistry Letters (2003), 13(5), 895-899
CODEN: BMCLE8; ISSN: 0960-894X
AB A series of phosphotyrosine containing cyclic peptides was designed and synthesized based upon the phage library derived cyclopeptide, G1TE. Considering the type-I β-turn feature of peptidic ligand binding to Grb2 SH2 domain, we introduce α,α-disubstituted cyclic amino acid, Ach, into the 4th position of the cyclic peptide to induce a local right handed 310 helical conformation. In order to stabilize the favorable binding conformation, the bulky and hydrophobic amino acids, neopentylglycine (NPG) and phenylalanine, were introduced into the 8th and 2nd positions of the peptide ligand, resp. To facilitate the sidechain of pTyr3 reaching into the phosphotyrosine binding pocket, a less bulky alanine was preferred in position 1. Based upon these global modifications, a highly potent peptide ligand was discovered with an IC50 = 1.68 nM, evaluated by ELISA binding essay. The ligand is at least 105 more potent than the lead peptide, termed G1TE.

L21 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 7
TI Potentiating effect of distant sites in non-phosphorylated cyclic peptide antagonists of the Grb2-SH2 domain
PY 2003
AU Long, Ya-Qiu; Guo, Ribo; Luo, Juliet H.; **Yang, Dajun**; **Roller, Peter P.**
SO Biochemical and Biophysical Research Communications (2003), 310(2), 334-340
CODEN: BBRCA9; ISSN: 0006-291X
AB Without the presence of a phosphotyrosyl group, a phage library derived non-phosphorylated cyclic peptide ligand of Grb2-SH2 domain attributed its high affinity and specificity to well-defined and highly favored interactions of its structural elements with the binding pocket of the protein. We have disclosed a significant compensatory role of the Glu2-sidechain for the absence of the phosphate functionality on Tyr0 in the peptide ligand, cyclo(CH2CO-Glu2--Leu-Tyr0-Glu-Asn-Val-Gly-Met5+-Tyr-Cys)-amide (termed G1TE). In this study, we report the importance of hydrophobic residue at the Tyr + 5 site in G1TE. Both acidic and basic amino acid substitutes are disfavored at this position, and replacement of Met with β-tert-butyl-Ala was found to improve the antagonist properties. Besides, the polarity of the cyclization linkage was implicated as important in stabilizing the favored binding conformation. Oxidation of the thioether linkage into sulfoxide facilitated the binding to Grb2-SH2 markedly. Simultaneous modification of the three distant sites within G1TE provided the best agent with an IC50 of 220 nM, which is among the most potent non-phosphorous- and non-phosphotyrosine-mimic containing Grb2-SH2 domain inhibitors yet reported. This potent peptidomimetic provides a novel template for the development of chemotherapeutic agents for the treatment of erbB2-related cancer. Biol. assays on G1TE(Gla2-) in which the original residue of Glu2- was substituted by γ-carboxyglutamic acid (Gla) indicated that it could inhibit the interaction between activated GF receptor and Grb2 protein in cell homogenates of MDA-MB-453 breast cancer cells at the 2 μM level. More significantly, both G1TE(Gla2-) alone and the conjugate of G1TE(Gla2-) with a peptide carrier can effectively inhibit intracellular association of erbB2 and Grb2 in the same cell lines with IC50 of 50 and 2 μM, resp.

L21 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
TI Flexibility of antideath protein Bcl-xL and the significance for designing small-molecule inhibitors
PY 2003
AU Wang, Shaomeng; Wang, Renxiao; Yang, Chao-Yie; Stuckey, Jeanne; Tomita, York; **Yang, Dajun**; Li, Peng; **Roller, Peter P.**; Sun, Haiying; Ding, Ke; Wang, Guoping; Tang, Guozhi; Chen, Jianyong; Zhang,

Manchao; Nikolovska-Coleska, Zaneta; Cao, Yeyu; Wu, Xihan
SO Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), COMP-131 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69DSA4
AB Bcl-xL is a potent antagonist of programmed cell death, or apoptosis, and is found to be overexpressed in many forms of cancer. Bcl-xL is considered as a highly promising mol. target for designing target-specific new anticancer drugs. Potent, non-peptidic, small mol. inhibitors of Bcl-xL may have a great therapeutic potential for the treatment of many forms of cancer by restoring the normal apoptosis machinery and by overcoming drug resistance in cancer cells. The binding site in Bcl-xL (the BH3 binding site) is highly flexible. Bcl-xL has very different conformations between its ligand-free and ligand-bound structures. It also adopts very different conformations dependent upon the size of the inhibitors it binds to (induced fit). The high-degree conformational flexibility of Bcl-xL makes it very difficult for the design of potent small mol. inhibitors for this protein using structure-based approach. In this presentation, we will describe our exptl. and computational investigations on the conformational flexibility of Bcl-xL and its implications to the design of small mol. inhibitors.

L21 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
TI Structure-based discovery of non-peptide, small molecule inhibitors of XIAP
PY 2003
AU Nikolovska-Coleska, Zaneta; Hu, Zengjian; Fang, Xueliang; Tomita, York; Zhang, Manchao; Xu, Liang; **Yang, Dajun**; Lippman, Marc E.; Li, Peng; **Roller, Peter P.**; Wang, Shaomeng
SO Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-106 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69EKY9
AB XIAP has a key function in the neg. regulation of apoptosis and overexpression of XIAP renders the cell resistant to a wide variety of apoptotic stimuli. Smac-based peptide inhibitors effectively could overcome apoptosis-resistance in different types of cancer cells with high levels of XIAP protein. Using the computer screening approach based on X-ray structure of XIAP, we discovered several classes of small mol. inhibitors of XIAP. One such inhibitor, SMXI-56, was studied in detail. SMXI-56 was shown to bind to the XIAP BIR3 domain, compete with the Smac peptide, and effectively inhibit cell growth and induce apoptosis in human prostate cancer cell lines with a high level of XIAP protein. SMXI-56 was shown to have minimal effect on normal epithelial prostate cells and other normal cells with low level of XIAP, showing selectivity. SMXI-56 was further shown to activate caspase-9 and -3. Our studies demonstrate that non-peptide, small mols. can directly and potently inhibit the anti-death function of XIAP and may be ultimately developed as new anticancer drugs by overcoming apoptosis-resistance in cancer cells.

L21 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
TI Design and synthesis of potent Grb2-SH2 domain antagonists based upon phage-library-derived cyclic peptide GlTE
PY 2003
AU Li, Peng; Zhang, Manchao; Peach, Megan L.; **Yang, Dajun**; **Roller, Peter P.**
SO Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-100 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69DSA4
AB Grb2 protein is an essential intracellular adapter protein involved in the activation of mitogenic Ras pathway. Development of Grb2-SH2 domain

antagonists is an effective approach to inhibit the growth of malignant cells by modulating the Grb2-related Ras signaling. Based upon the phage library derived cyclopeptide, G1TE, a variety of potent non-phosphorylated Grb2-SH2 domain antagonists were designed and synthesized by the constraint of backbone conformation and modification of amino acid sidechains of G1TE analogs. Based upon these SAR studies, a series of Pmp-containing Grb2-SH2 domain antagonists were also developed. Some of these phosphatase stable analogs exhibit sub-nanomolar inhibitory activity. These extremely potent compds. provide novel and ideal templates for the development of Grb2-SH2 domain antagonists, and act as chemotherapeutic leads for the treatment of erbB2-related cancer.

=> d l21 11-20 ti au py abs

L21 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 8
TI Molecular mechanism of gossypol-induced cell growth inhibition and cell death of HT-29 human colon carcinoma cells
AU Zhang, Manchao; Liu, Hongpeng; Guo, Ribo; Ling, Yan; Wu, Xiaojin; Li, Bihua; **Roller, Peter P.**; Wang, Shaomeng; **Yang, Dajun**
PY 2003
AB Gossypol, a male contraceptive drug, has been demonstrated to have antiproliferative and antimetastatic effects on many kinds of cancer cells in vitro. HT-29 human carcinoma cell line is one of the most susceptible cell lines to gossypol-induced cell death. Here, it is shown that treatment of HT-29 cells with gossypol not only induces cell cycle arrest on the G0/G1 phase, but also induces apoptosis. With a serial of Western blot anal., it is revealed that gossypol-induced cell cycle arrest is involved in P21 up-regulation and cyclin D1 down-regulation; gossypol-induced apoptosis triggers down-regulation of anti-apoptosis Bcl-2 members: Bcl-XL, Bag-1 and Mcl-1, up-regulation of pro-apoptosis Bcl-2 member Bak, activation of caspase-3, -6, -7, -8, and -9, up-regulation of Apaf-1, release of cytochrome c (cyto-c) from mitochondria, and activation of both DFF45 and PARP. Taken together, gossypol-induced cell death initiates extensive alterations of cell cycle and apoptosis proteins. Gossypol-induced apoptosis of HT-29 cells is through first the mitochondrial pathway, then the death receptor pathway, and the mitochondria pathway is, at least in part, involved in cyto-c release.

L21 ANSWER 12 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI Structure-based discovery of non-peptide, small molecule inhibitors of XIAP.
AU Nikolovska-Coleska, Zaneta [Reprint Author]; Hu, Zengjian [Reprint Author]; Fang, Xueliang [Reprint Author]; Tomita, York; Zhang, Manchao; Xu, Liang; **Yang, Dajun**; Lippman, Marc E.; Li, Peng; **Roller, Peter P.**; Wang, Shaomeng [Reprint Author]
PY 2003

L21 ANSWER 13 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI Design and synthesis of potent Grb2-SH2 domain antagonists based upon phage library derived cyclic peptide G1TE.
AU Li, Peng [Reprint Author]; Zhang, Manchao; Peach, Megan L. [Reprint Author]; **Yang, Dajun**; **Roller, Peter P.** [Reprint Author]
PY 2003

L21 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
TI Structure-based design and synthesis of thioether-bridged cyclic peptides as highly potent Grb2-SH2 domain inhibitors

AU Li, Peng; Li, Bihua; Zhang, Manchao; **Yang, Dajun; Roller, Peter P.**

PY 2002

AB Growth factor receptor-bound protein 2(Grb2) is an essential intracellular adapter protein, which mediates intracellular signaling through the oncogenic erbB2 receptor. Based upon the phage library generated Grb2-SH2 domain inhibitor G1TE, we have developed a number of redox stable cyclic peptides that selectively inhibit the association of ErbB2 receptor with the Grb2-SH2 domain, with IC50 as low as 36 nM. Peptidomimetic modification of the key amino acid residues, such as GluY-2, LeuY-1, Tyr0, GluY+1, ValY+3 and MetY+5 in these peptides was investigated to study the relationship between the three-dimensional structures and activities of these inhibitory agents, with the intention of developing more drug-like agents with enhanced therapeutic effectiveness.

L21 ANSWER 15 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

TI Structure-based design and synthesis of thioether-bridged cyclic peptides as highly potent Grb2-SH2 domain inhibitors.

AU Li, Peng [Reprint author]; Li, Bihua; Zhang, Manchao; **Yang, Dajun ; Roller, Peter P.** [Reprint author]

PY 2002

L21 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 9

TI Discovery of Small-Molecule Inhibitors of Bcl-2 through Structure-Based Computer Screening

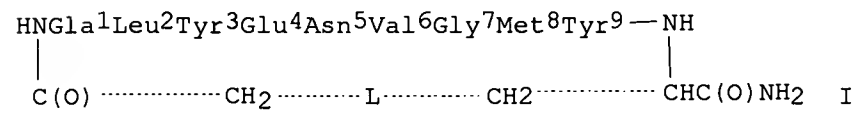
AU Enyedy, Istvan J.; Ling, Yan; Nacro, Kassoum; Tomita, York; Wu, Xihan; Cao, Yeyu; Guo, Ribo; Li, Bihua; Zhu, Xiaofeng; Huang, Ying; Long, Ya-Qiu; **Roller, Peter P.; Yang, Dajun**; Wang, Shaomeng

PY 2001

AB Bcl-2 belongs to a growing family of proteins which regulates programmed cell death (apoptosis). Overexpression of Bcl-2 has been observed in 70% of breast cancer, 30-60% of prostate cancer, 80% of B-cell lymphomas, 90% of colorectal adenocarcinomas, and many other forms of cancer. Thereby, Bcl-2 is an attractive new anti-cancer target. Herein, we describe the discovery of novel classes of small-mol. inhibitors targeted at the BH3 binding pocket in Bcl-2. The three-dimensional (3D) structure of Bcl-2 has been modeled on the basis of a high-resolution NMR solution structure of Bcl-XL, which shares a high sequence homol. with Bcl-2. A structure-based computer screening approach has been employed to search the National Cancer Institute 3D database of 206 876 organic compds. to identify potential Bcl-2 small-mol. inhibitors that bind to the BH3 binding site of Bcl-2. These potential Bcl-2 small-mol. inhibitors were first tested in an in vitro binding assay for their potency in inhibition of the binding of a Bak BH3 peptide to Bcl-2. Thirty-five potential inhibitors were tested in this binding assay, and seven of them were found to have a binding affinity (IC50 value) from 1.6 to 14.0 M. The anti-proliferative activity of these seven active compds. has been tested using a human myeloid leukemia cell line, HL-60, which expresses the highest level of Bcl-2 protein among all the cancer cell lines examined The most potent compound had an IC50 value of 4 μM in inhibition of cell growth using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Five other compds. had moderate activity in inhibition of cell growth. The most active compound was further evaluated for its ability to induce apoptosis in cancer cells. It was found that this compound induces apoptosis in cancer cells with high Bcl-2 expression and its potency correlates with the Bcl-2 expression level in cancer cells. Furthermore, using NMR methods, we conclusively demonstrated that this most active compound binds to the BH3 binding site in Bcl-XL. Our results showed that small-mol. inhibitors of Bcl-2 modulate the biol. function of Bcl-2, and induce apoptosis in cancer cells with high Bcl-2 expression, while they have little effect on cancer cells with low or undetectable levels of

Bcl-2 expression. Therefore, this active compound can be used as a valuable pharmacol. tool to elucidate the function of Bcl-2 and also serves as a novel lead compound for further design and optimization. Our results suggest that the structure-based computer screening strategy employed in the study is effective for identifying novel, structurally diverse, nonpeptide small-mol. inhibitors that target the BH3 binding site of Bcl-2.

L21 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
TI Redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein, conjugates thereof, compositions, methods of synthesis, and use
IN **Roller, Peter P.**; Long, Ya-Qui; Lung, Feng-Di T.; King, C. Richter; **Yang, Dajun**
PY 2000
2001
2003
GI



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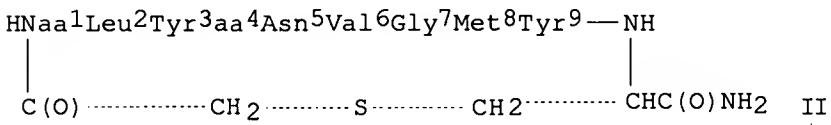

II

AB The invention provides I (L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Glu4, Val6, Met8 and Tyr9 is modified). Also provided is compound II [aa1 = Adi and aa4 = Glu, or each of aa1 and aa4= Adi; L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Val6, Met8 and Tyr9 is modified]. The above compds. (and their conjugates) bind to an SH2 domain in a protein comprising an SH2 domain, are non-phosphorylated, are redox-stable in vivo, and are characterized by an IC50 in vivo of less than about 4.0 <mM with respect to the SH2 domain in Grb2. Upon binding to the SH2 domain of Grb2, a compound as described above has a turn conformation. Optionally, there is a conservative or neutral amino acid substitution at either one or both of Leu2 and Gly7. Also provided are a conjugate comprising a compound as described above and a carrier agent, a composition comprising (i) a compound or a conjugate as described above and (ii) a carrier, a method of inhibiting binding of an SH2 domain in a protein comprising an SH2 domain to a target protein in an animal, wherein the SH2 domain is contacted with a target protein-binding inhibiting effective amount of a compound or a conjugate as described above, and a method of synthesizing such conjugates.

L21 ANSWER 18 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI High affinity nonphosphorylated cyclic peptide inhibitors of Grb2-SH2/growth factor receptor interactions.
AU Long, Ya-Qiu [Reprint author]; Lung, Feng-Di T.; Voigt, Johannes H. [Reprint author]; Yao, Zhu-Jun [Reprint author]; Burke, Terrence R., Jr. [Reprint author]; **Yang, Dajun**; Luo, Juliet H.; Guo, Ribo; Richter King, C.; **Roller, Peter P.** [Reprint author]
PY 2000

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PY 2000
AB Structure-activity studies provide two non-phosphorylated cyclic peptides with sub-micromolar binding affinities to Grb-SH2. Oligino et al. have previously reported the discovery of a novel non-phosphorylated cyclic peptide (G1), based on phage library methodologies. Earlier efforts of the authors have indicated that the binding affinity of closely related cyclic peptide variants of G1 was exquisitely sensitive to ring size modifications. It was found that one thioether cyclized analog (G1TE) was equipotent to the lead peptide G1. Biol. assays on G1TE(Gla1) (V) demonstrated that it inhibits activated GF-receptor/Grb2 protein-protein interactions in cell homogenates of MDA-MB-453 breast cancer cells at the 1-3 μM level. Peptide V, conjugated to peptide carriers, inhibited MAP kinase activation in the same cell line at 25 μM concentration The agents hereby described may provide new pharmacophore models for the development of highly selective peptidomimetic variants of Grb2 antagonists.

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TI Structural Requirements for Tyr in the Consensus Sequence Y-E-N of a Novel Nonphosphorylated Inhibitor to the Grb2-SH2 Domain
AU Long, Ya-Qiu; Yao, Zhu-Jun; Voigt, Johannes H.; Lung, Feng-Di T.; Luo, Juliet H.; Burke, Terrence R., Jr.; King, C. Richter; **Yang, Dajun ; Roller, Peter P.**
PY 1999
AB The phage library derived, nonphosphorylated and thioether-cyclized peptide, termed G1TE, cyclo(CH2CO-Glu1-Leu-Tyr3-Glu-Asn-Val-Gly-Met-Tyr-Cys10)-amide, represents a new structural motif that binds to the Grb2-SH2 domain in a pTyr-independent manner, with an IC50 of 20 μM. The retention of binding affinity is very sensitive with respect to peptide ring-size alterations and Ala mutations. We demonstrated previously that the Glu1 side chain and its closely related analogs partially compensate for the absence of the phosphate functionality on Tyr3, and, based on mol. modeling, these acidic side-chains complex with the Arg67 and Arg86 side-chains of the protein in the binding cavity. In this study we judiciously altered and incorporated various natural and unnatural amino acids as Tyr replacements within the -YEN- motif, and we demonstrate the functional importance and structural requirement of Tyr3 for effective binding of this novel non-phosphorylated ligand to the Grb2-SH2 domain. The Ph side-chain moiety and a polar functional group with specific orientation in position Y3 of the peptide are particularly required. Using SPR binding assays, a submicromolar inhibitor (IC50 = 0.70 μM) was obtained when Glu1 was replaced with α-aminoadipate and Tyr3 was replaced with 4-carboxymethyl-Phe, providing peptide G1TE(Adi1, cmPhe3). This peptide also inhibited Grb2/p185erbB-2 protein association in cell homogenates of erbB-2-overexpressing MDA-MA-453 cancer cells at .apprx. 1μM concns. (c) 1999 Academic Press.